

## PATENT

Attorney Docket No. 039592-5113

reaction as either a neutral thiol, R"SH, and an appropriate base or, more preferably, as a salt of a thiolate anion, R"S<sup>-</sup>, with a corresponding counterion, M<sup>+</sup>, of sodium, potassium, ammonium and the like. R" may be a C<sub>1</sub>-C<sub>10</sub> alkyl group or a C<sub>4</sub>-C<sub>10</sub> aryl or heteroaryl group containing at least one heteroatom of N, O or S. As discussed here, R" may be linear or branched, substituted or unsubstituted. Possible substituents include, but are not limited to, alkyl, alkenyl, alkynyl, hydroxy, cyano, ether, and thioether groups. Examples of suitable R" groups include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, phenyl, and naphthyl groups. Preferably, the thiolate anion is sodium thiomethoxide.

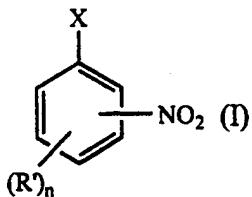
Conversion of the nitro-substituted aromatic carboxylic acid ester 2 to the thioether-substituted aromatic carboxylic acid ester 3 may be performed by any means that promotes displacement of the nitro group with a thioether group. Preferably, such conversion is conducted in a homogeneous solvent system or a phase-transfer solvent system. More preferably, such conversion is conducted in a phase-transfer solvent system. A homogeneous solvent system is based on a mixture of water and a water-soluble solvent. Suitable water-soluble solvents include, but are not limited to, ketones (e.g. acetone or other dialkyl ketones), lower alcohols (e.g. C<sub>1</sub>-C<sub>4</sub> alcohols), formamide, dimethyl formamide, dimethyl sulfoxide, N-methylpyrrolidone and the like and mixtures thereof. A phase-transfer solvent system is based on a phase transfer catalyst in a water-immiscible solvent and, optionally, water. Water-immiscible solvents include aliphatic hydrocarbons (e.g. hexane, heptane, octane), aromatic hydrocarbons (e.g. toluene, xylenes, chlorobenzene), cyclic or acyclic ethers (e.g. tert-butyl methyl ether, diisopropyl ether, diethoxymethane) and mixtures thereof. The phase-transfer catalyst is chosen from readily available ammonium or phosphonium salts such as tetrabutylammonium bromide, tetrabutylammonium chloride, methyltributylammonium chloride, methyl trioctylammonium chloride, tetrabutylphosphonium bromide and the like. Preferably, the phase transfer catalyst is tetrabutylammonium bromide.

The temperature of and the length of time for the reaction of a nitro-substituted aromatic carboxylic acid ester 2 with a thiolate anion, as described above, to form a thioether-substituted

heteroatom of N, O, or S. Examples of suitable aryl groups include, for example, phenyl, benzyl, naphthyl, furyl, benzofuranyl, pyranyl, pyrazinyl, thienyl, pyrrolyl, imidazolyl, pyridyl, pyrimidinyl, pyridazinyl, indolyl, indolizinyl, indazolyl, purinyl, isoquinolyl, quinolyl, isothiazolyl, isoxazolyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzothienyl, isoindolyl, anthryl, phenanthryl, and the like. The aryl group (Ar) of the nitro-substituted aryl halide 1 may also be further substituted with, for example, substituents R'. As discussed here, R' may be linear or branched, substituted or unsubstituted. Possible R' substituents include, but are not limited to, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>2</sub>-C<sub>10</sub> alkynyl, C<sub>4</sub>-C<sub>10</sub> aryl or heteroaryl, ether, thioether, nitro, trifluoromethyl, fluoro, cyano, and acyl group.

According to the invention, the nitro-substituted aryl halide 1 contains at least one nitro group. Any one nitro group may be adjacent to or at any other position relative to the halo group on the aryl group. For example, if the aryl group is a phenyl group, a nitro group may be substituted at the ortho-, meta-, or para- position. In a preferred embodiment of the invention, the nitro-substituted aryl halide 1 is an ortho-substituted aryl halide, *i.e.* at least one nitro group is ortho to the halo group.

In a preferred embodiment of the invention, the nitro-substituted aryl halide 1 is a nitro-substituted aryl halide of formula (I):



In formula (I), X is a halo group as described above, n is an integer from 1-4, and R' is, independently, as described above or may together with the phenyl group form a substituted or unsubstituted fused polycyclic ring system. In a more preferred embodiment of the invention, in formula (I), n is 1 and R' is a trifluoromethyl group. In another more preferred embodiment of